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National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Sacubitril valsartan for treating chronic heart failure

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Novartis	Yes, it would be appropriate to refer this topic to NICE for a Single Technology Appraisal, especially as sacubitril valsartan has been granted a positive Promising Innovative Medicine (PIM) designation from the MHRA.	Comment noted
	Pumping Marvellous	Yes.	Comment noted
	Servier	Yes	Comment noted
Wording	Novartis	The remit should be amended to reflect the exact wording of the proposed indication and generic name of LCZ696: 'To appraise the clinical and cost effectiveness of sacubitril valsartan within its marketing authorisation for treating heart failure (NYHA class II-IV) with systolic dysfunction'.	Comment noted. The remit has been updated to read: 'To appraise the clinical and cost effectiveness of sacubitril valsartan within its marketing authorisation for

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			treating heart failure (NYHA class II-IV) with systolic dysfunction'.
	Pumping Marvellous	It reflects the issues.	Comment noted.
	Servier	Yes	Comment noted.
Timing Issues	Novartis	There is an urgent need for guidance to be issued as soon as possible, as this technology has the potential to address a significant unmet need in the management of chronic heart failure (CHF) in the UK. The accelerated EMA regulatory timings and PIM designation recognise this unmet need. Despite improving implementation of NICE clinical guidelines and recommended treatments for CHF over the past five years, mortality and hospitalisation rates are still high in UK patients with heart failure[1]. In 2012-2013, almost one in seven patients died during hospitalisation for heart failure or in the month following discharge[1]. Sacubitril valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) proven to be superior to current standard of care, ACE inhibition, by significantly reducing the risk of all-cause and cardiovascular (CV) mortality and reducing risk of hospitalisations due to heart failure[2]. Sacubitril valsartan also improves quality of life in patients and reduces symptoms of heart failure compared to ACE inhibition[2].The pivotal trial PARADIGM-HF was terminated prematurely due to the overwhelming benefit of sacubitril valsartan compared to the ACE inhibitor, enalapril. As a result, sacubitril valsartan was the first investigational cardiovascular medicine ever to be granted accelerated regulatory assessment by the EMA. Sacubitril valsartan has recently received a positive PIM designation from the MHRA. This is an early indication that this technology is a promising candidate for the Early Access to Medicines Scheme (EAMS), intended for	Comments noted.

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		the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition with the potential to address an unmet medical need. This is the first time a cardiovascular product and any non-oncology product has been awarded a PIM designation. Novartis is concerned about the potential for a significant gap between marketing authorisation for sacubitril valsartan and NICE guidance being issued, which we estimate could be up to 10 months based on current estimates and 7 months after expected SMC guidance, preventing access to patients who could benefit from this medicine. Due to the accelerated regulatory timings, and assuming positive EAMS scientific opinion for sacubitril valsartan, we expect the opportunity for patients to benefit from EAMS to be unfortunately limited to 1-2 months until marketing authorisation. We therefore feel it is important for NICE to 'fast track' this appraisal in order to minimise this gap and allow patients to access to this innovative medicine as soon as possible following marketing authorisation. In order to expedite timelines, we would appreciate NICE exploring with the Department of Health whether medicines participating in EAMS could be automatically referred to NICE. This approach would be consistent with the draft EAMS operational guidance document. Reference 1: National Heart Failure Audit (2012-13) Reference 2: McMurray et. al. (2014) Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF) New Eng J Med, 371:993-1004	
	Pumping Marvellous	It is a priority for the NHS to adopt innovative therapies to help the QOL of HF patients in the UK.	Comment noted.
	Servier	Timing should be scheduled with the marketing authorisation of LCZ696 in mind, to ensure timely advice to the NHS.	Comment noted. The technology appraisal programme aims to issue guidance within 6 months of the marketing

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			authorisation being granted, and the timing of appraisals are scheduled to be aligned accordingly.
Additional comments on the draft remit	Servier	None.	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis	Additionally, prevalence data demonstrates that approximately 50% of patients with CHF in the UK have systolic dysfunction[1]. Reference 1: Udelson (2011) Heart Failure with Preserved Ejection Fraction. Circulation. 2011;124:e540-e543	Comment noted. We have updated the scope to indicate the proportion of people with heart failure left ventricular ejection fraction from the National Heart Failure Audit (2012/2013). The scope reads:

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			Approximately 42,000 people were admitted to hospital in England with heart failure in 2012/13 and 72% of these people had reduced left ventricular ejection fraction.
	Pumping Marvellous	Yes	Comment noted.
	Servier	Yes. However, NICE TA267 indicates that that standard therapy for heart failure includes beta-blockers, ACE inhibitors and mineralocorticoid receptor antagonists. Therefore this should be appropriately reflected in the background information.	The text: 'in clinical practice, an aldosterone agonist is usually administered alongside other treatments' has been added to the background section of the scope.
The technology/ intervention	Novartis	LCZ696 should be referred to by its generic name sacubitril valsartan.	Comment noted. The scope has been updated accordingly.
	Pumping Marvellous	Yes	Comment noted.
	Servier	Yes	Comment noted.
Population	Novartis	The population should be defined as: 'People with heart failure (NYHA class	Comment noted. At the

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		II-IV) with systolic dysfunction' in order to align with wording from the proposed indication submitted to the EMA. The PARADIGM-HF study demonstrates consistently superior clinical endpoints (both primary and secondary) for sacubitril valsartan compared to ACE inhibition across all pre-specified trial sub-groups so there are no sub-groups of people in which sacubitril valsartan is expected to be more clinically effective or cost effective.	scoping workshop it was noted that the proposed indication submitted by the company to the EMA was broader than that studied in clinical trials. The population has been updated to align with the population outlined in the remit that is, people with chronic heart failure (NYHA class II-IV) with systolic dysfunction. It is noted that the recommendations will be made in accordance with the marketing authorisation.
	Pumping Marvellous	We believe the population is defined. We cannot identify sub groups to this population.	Comment noted.
	Servier	Population should be more clearly defined as: Adults with chronic heart failure due to left ventricular systolic dysfunction of ischaemic or non-ischaemic origin, who have been prescribed standard optimal heart failure therapy. LCZ696 has only been studied in patients with a left ventricular ejection fraction of 35% or lower, the appraisal should be limited to this group of patients.	Comment noted. The population has been updated to people with chronic heart failure (NYHA class II-IV) with systolic dysfunction to reflect the remit for this

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			appraisal. It is noted that the recommendations will be made in accordance with the marketing authorisation.
Comparators	Novartis	NICE chronic heart failure guidelines (CG 108) recommend ACE inhibitors licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction as a first-line therapy1. As the proposed positioning for sacubitril valsartan in the treatment pathway for heart failure is as first-line therapy, ACE inhibitors licensed for heart failure should be considered the key comparator to sacubitril valsartan. This is further supported by the NICE Scientific Advice report to Novartis (2009) which stated that it was appropriate for an ACE inhibitor to be the comparator in both the clinical trial and economic analysis of sacubitril valsartan. Angiotensin II receptor blockers (ARBs) licensed for heart failure are recommended as alternative first-line therapy options in patients who are intolerant to ACE inhibition, according to NICE clinical guidelines (CG 108)1. Given the order of ACE inhibitors and ARBs in the treatment pathway for heart failure, ARBs should only be a relevant comparator for patients who have intolerable side effects with ACE inhibitors. No head-to-head clinical trial data is currently available for sacubitril valsartan compared to ARBs in patients with heart failure with systolic dysfunction. In summary, ACE inhibitors can be described as the 'best alternative care' provided in the NHS. However, as CG 108 clearly describes best clinical practice in the UK, we propose that the comparator in the scope is defined as 'standard therapy without sacubitril valsartan'[2]. Reference 1: National Institute for Health and Care Excellence (2010) Chronic heart failure: Management	Comments noted. The scope had been updated. The comparators are: ACE inhibitor in combination with standard care Angiotensin II receptor blocker in combination with standard care (for people in whom an ACE inhibitor is unsuitable). Standard care includes treatment with a beta blocker and aldosterone antagonist.

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		of chronic heart failure in adults in primary and secondary care. NICE Clinical guideline 108. Footnote 2: The majority of patients with heart failure are adhering to NICE clinical guideline CG 108 in the UK. Upon discharge for systolic dysfunction, 73% of patients are prescribed ACE inhibitors, 18% are prescribed ARBs and 82% are prescribed beta-blockers. 85% of patients are prescribed either an ACEi or an ARB. Based on data from National Heart Failure Audit (2012/13).	
	Pumping Marvellous	Yes.	Comment noted.
	Servier	The treatment of chronic heart failure due to left ventricular systolic dysfunction has been robustly studied and is well established. ACE inhibitors and Angiotensin II receptor inhibitors are clearly established within standard therapy alongside beta-blockers, mineralocorticoid receptor antagonists and other NICE approved therapies such as ivabradine, ICDs etc. LCZ696 plus other optimal standard therapy (beta-blockers, mineralocorticoid receptor antagonists etc.) should therefore be compared to ACE inhibitors/Angiotensin II receptor inhibitors plus other optimal standard therapy.	Comments noted. The scope has been updated. Sacubitril valsartan in combination with standard care (including treatment with a beta blocker and an aldosterone antagonist) will be compared with: ACE inhibitor in combination with standard care Angiotensin II receptor blocker in combination with standard care (for people in whom an ACE inhibitor is unsuitable. Standard care includes treatment with a beta blocker and aldosterone

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			antagonist.
Outcomes	Novartis	Generally, yes, however we suggest that outcomes for all-cause mortality and all-cause hospitalisation should also be specified in the scope.	Comment noted. All-cause mortality is included in the scope as 'mortality'. All-cause hospitalisation has been added as an additional outcome in the scope.
	Pumping Marvellous	Yes	Comment noted.
	Servier	Yes. Symptoms of heart failure will be captured within health related quality of life. Therefore this should not be considered as a separate outcome measure.	Comment noted. Health related quality of life is a measure of the extent to which symptoms affect quality of life and as such is a separate measure to symptoms of heart failure.
Economic analysis	Novartis	No comments.	Comment noted.
	Pumping Marvellous	No comment	Comment noted.
Equality and Diversity	Novartis	No comments.	Comment noted.
	Pumping Marvellous	It is compliant	Comment noted.

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Section	Consultee/ Commentator	Comments [sic]	Action
Innovation	Novartis	Novartis considers sacubitril valsartan to be a step-change innovation in the management of heart failure (NYHA class II-IV) with systolic dysfunction. As detailed above, sacubitril valsartan has recently received a positive PIM designation from the MHRA. This is an early indication that this technology is a promising candidate for EAMS, intended for the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition with the potential to address an unmet medical need. One of the key criteria a technology needs to fulfill in order to receive a PIM designation is the likelihood of offering a major advantage over therapies/methods currently used in the UK to treat the particular condition. Sacubitril valsartan is the first cardiovascular medicine and first non-oncology medicine to be awarded a PIM designation as well as accelerated regulatory assessment by the CHMP. This is due to the superior efficacy of sacubitril valsartan demonstrated in the PARADIGM-HF trial when compared to standard of care (ACE inhibition) which was terminated prematurely due to overwhelming benefit of sacubitril valsartan. No significant and substantial health-related benefits that are unlikely to be included in the QALY calculation have been identified at this stage, however economic modelling is ongoing.	Comments noted.
	Pumping Marvellous	The technology LCZ is an innovative therapy which we believe, through the trial data will have a significant impact on the QOL of heart failure patients under the NHS remit. The trial results around mortality and hospitalisation suggest this is a step change therapy. We do not believe that due to its method of calculation that the QALY takes into account patient opinion and patient QOL state in its calculations.	Comments noted. The Appraisal Committee will take into account any benefits of sacubitril valsartan highlighted by the patient and professional groups or the company that are

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		Refer to PARADIGM-HF trial.	not included in the QALY calculations in its considerations.
Other considerations	Novartis	No comments	Comment noted.
	Pumping Marvellous	Nil	Comment noted.
	Royal College of Pathologists	The appraisal group needs to be aware that neutral endopeptidase (NEP) inhibitors will affect levels of B type natriuretic peptides, raising them. This may have a significant impact on the existing NICE guidelines for diagnosis of acute and chronic heart failure, potentially making them invalid in patients treated with NEP inhibitors.	Comment noted. The NICE technology appraisals team will liaise with the NICE clinical guidelines team about how the recommendations for sacubitril valsartan impact the clinical guideline.
Questions for consultation	Novartis	We feel it is appropriate to refer this topic to NICE through the Single Technology Appraisal process.	Comment noted.
Additional comments on the draft scope	Novartis	No further comments.	Comment noted.
	British Hypertension Society	Important to note that LCZ696 lowers blood pressure, and may be particularly useful in patients with a history of hypertension. Throughout the recent major trial, the BP was lower in the LCZ696-treated group, when compared to an ACE inhibitor alone.	Comment noted.

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Section	Consultee/ Commentator	Comments [sic]	Action
	Servier	None	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Merck Sharpe Dohme
Boehringer Ingelheim
Department of Health
Royal College of Nurses

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed:					
Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:

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1.	HEART UK	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore HEART UK have been added to the matrix under 'patient/carer' groups.
2.	British Nuclear Cardiology Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the British Nuclear Cardiology Society have been added to the matrix under 'professional groups'.

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3.	British Society of Cardiovascular Imaging	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the British Society of Cardiovascular Imaging have been added to the matrix under 'professional groups'
4.	Antithrombotic Trialists' (ATT) Collaboration	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the Antithrombotic Trialists' (ATT) Collaboration have been added to the matrix under 'relevant research groups'
5.	Muslim Health Network	PIPP		Removed	The organisation has disbanded and was removed from the matrix under 'patient/carer groups'